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(54) Title: ACIDS AND ACID SALTS AND THEIR USE IN DELIVERY SYSTEMS

(57) Abstract

The present invention relates to a delivery system, and in particular to carboxylic acids for use as a delivery system of sensitive agents such as bioactive peptides. The carboxyl acids and salts can form non-covalent mixtures with active biologically-active agents. These mixtures are suitable for oral administration of biologically active agents to animals.

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ACIDS AND ACID SALTS AND THEIR USE IN DELIVERY SYSTEMS

The present invention relates to compositions suitable for drug delivery, and in particular to compositions in which carboxylic acids and salts are used as carriers for biologically-active agents, including, but not limited to, bioactive peptides and the like. The acids and salts can form non-covalent mixtures with biologically-active agents and are suitable for oral administration to animals. Methods for the preparation and for the administration of such compositions are also disclosed.

Background of the Invention

Conventional means for delivering biologically-active agents, including, but not limited to, pharmaceutical and therapeutic agents to animals often are severely limited by chemical and physical barriers imposed by the body. Oral delivery of many biologically-active agents would be the route of choice if not for the presence of chemical and physico-chemical barriers such as extreme and varying pH in the gastro-intestinal (GI) tract, exposure to powerful digestive enzymes, and impermeability of gastro-intestinal membranes to the active ingredient. Among the numerous pharmacological agents which are are not suitable for oral administration are biologically-active peptides such as calcitonin and insulin. Examples of other compounds which are affected by the physico-chemical barriers are polysaccharide mucopolysaccharides, including, but not limited to, heparin, heparinoids, antibiotics and other organic substrates. These agents are rapidly destroyed in the

gastro-intestinal tract by acid hydrolysis, enzymes, or the like.

Prior methods for orally administering vulnerable pharmacological agents have relied on co-administration of adjuvants (*e.g.*, resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether) to increase artificially the permeability of the intestinal walls; and on co-administration of enzymatic inhibitors (*e.g.*, pancreatic trypsin inhibitor, diisopropylfluorophosphate (DFF) and trasylol) to avoid enzymatic degradation. Liposomes have also been described as drug delivery systems for insulin and heparin. See, for instance, U.S. Patent No. 4,239,754; Patel et al. (1976) FEBS Letters Vol. 62, page 60; and Hashimoto et al. (1979) Endocrinol. Japan, Vol. 26, page 337. The broader use of the aforementioned methods, however, as drug delivery systems are precluded for reasons which include: (1) the use of toxic amounts of adjuvants or inhibitors; (2) the lack of suitable low MW cargoes; (3) the poor stability and inadequate shelf life of the systems; (4) difficulty in manufacturing; and (5) the failure of the systems to protect the active ingredient; and (6) the failure of the systems to promote absorption of the active agent.

More recently, microspheres of artificial polymers or proteinoids of mixed amino acids have been described for delivery of pharmaceuticals. For example, U.S. Patent No. 4,925,673 describes such microspheres as well as methods for their preparation and use. The proteinoid microspheres of the '673 patent are useful for encapsulating a number of active agents.

There is a need in the art for a simple and inexpensive delivery system which is easily prepared and which can deliver a broad range of biologically-active agents.

Summary of the Invention

Compositions for orally delivering biologically-active agents incorporating acids and acid salts as carriers are provided.

A composition comprising;

(A) at least one biologically-active agent; and

(B) (a) a compound having the formula:

$$R—CO_2H$$

wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)-naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and naphthyl(C_2 to C_{10} alkenyl);

R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, $-CO_2R^1$, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alk)aryl, aral(C_1 to C_{10})alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl;

(b) a salt thereof; or

(c) a combination of (a) and (b).

In an alternative embodiment, these compositions are used in oral dosage unit forms. The compositions or oral dosage unit forms be orally administrated to animals.

Description of the Drawings

Figure 1 is a graphic illustration of the results of oral gavage testing in rats using calcitonin with cyclohexanepropanoic acid carrier.

Figures 2 and 3 are graphic illustrations of the results of oral gavage testing in rats using heparin with cyclohexanepropanoic acid and cyclohexane carboxylic acid carriers.

Figure 4 is a graphic illustration of the results of oral gavage testing in rats using heparin with cycloheptane-

carboxylic acid, cyclohexanecarboxylic acid and cyclopentane-carboxylic acid carriers.

Figures 5 and 6 are graphic illustrations of the effects of varying the carrier loading and the cargo loading in oral gavage testing in rats using heparin with cyclohexanepropanoic acid carrier.

Detailed Description of the Invention

Carboxylic acids and salts of carboxylic acids may be used as carriers to deliver biologically-active agents, such as peptides, mucopolysaccharides, carbohydrates, lipids and pesticides. These carriers are particularly useful in facilitating the delivery of orally sensitive biologically-active agents. For example, hormones such as calcitonin, insulin and polysaccharides such as heparin, are not considered orally administrable for various reasons. Insulin, for example, is sensitive to the denaturing conditions of the gastrointestinal (GI) tract. Also, heparin, by virtue of its charge and hydrophilic nature, is not readily absorbed from the gastro-intestinal tract.

The compositions of the subject invention are useful for administering biologically-active agents to any animals such as birds; mammals, such as primates and particularly humans; and insects.

The present invention, in several embodiments, uses readily available and inexpensive starting materials and provides a cost-effective method for preparing and isolating acids or salts thereof. The method is simple to perform and is amenable to industrial scale-up for commercial production.

Biologically-active agents suitable for use with carriers disclosed herein include, but are not limited to, peptides, and particularly small peptide hormones, which by themselves pass slowly or not at all through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastrointestinal tract; polysaccharides and particularly mixtures of mucopolysaccharides, carbohydrates; lipids; or any combination thereof. Examples include, but are not limited to, human

growth hormone; bovine growth hormone; growth hormone releasing hormone; interferons; interleukin-I; insulin; heparin, and particularly low molecular weight heparin; calcitonin; erythropoietin; atrial naturetic factor; antigens; monoclonal antibodies; somatostatin; adrenocorticotropin; gonadotropin releasing hormone; oxytocin; vasopressin; vancomycin; cromylyn sodium; desferrioxamine (DFO); or any combination thereof.

The carboxylic acids of the present invention have the formula: $R-CO_2H$

wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)-naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and naphthyl(C_2 to C_{10} alkenyl);

R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, $-CO_2R^1$, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alk)aryl, aral(C_1 to C_{10})alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl.

The preferred carboxylic acids are cyclohexanecarboxylic acid, cyclopentanecarboxylic acid, cycloheptanecarboxylic acid, hexanoic acid, 3-cyclohexanepropanoic acid, methylcyclohexanecarboxylic acid, 1,2-cyclohexanedicarboxylic acid, 1,3-cyclohexanedicarboxylic acid, 1,4-cyclohexanedicarboxylic acid, 1-adamantanecarboxylic acid, phenylpropanoic acid, adipic acid, cyclohexanepentanoic acid, cyclohexanebutanoic acid, pentylcyclohexanoic acid, 2-cyclopentanehexanoic acid, cyclohexanebutanoic acid, and (4-methylphenyl) cyclohexane acetic acid.

Additionally the carriers of the present invention can be used to deliver other active agents such as pesticides and the like.

In one embodiment, acids and salts thereof may be used directly as a drug delivery carrier by simply mixing the acids or salts with the active ingredient prior to administration. The acids and salts of the invention are particularly useful for the oral administration of certain biologically-active agents, *e.g.*, small peptide hormones, which, by themselves, do not pass or only pass slowly through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage in the gastrointestinal tract.

The carboxylic acids and salts of the invention do not alter the physiological and biological properties of the active agent. The system is particularly advantageous for delivering chemical or biological agents which otherwise would be destroyed or rendered less effective by conditions encountered within the body of the animal to which it is administered, before the agent reaches its target zone and pharmacological agents which are poorly absorbed in the gastro-intestinal tract. The target zones can vary depending upon the drug employed.

Typically, the compositions of the present invention are prepared by mixing an aqueous solution of the carrier with an aqueous solution of the active ingredient, just prior to administration. Alternatively, the carrier and biologically active ingredient can be admixed during the manufacturing process. The solutions may optionally contain additives such as phosphate buffer salts, citric acid, acetic acid, gelatin and gum acacia.

In practicing the invention, stabilizing additives may be incorporated into the carrier solution. With some drugs, the presence of such additives promotes the stability and dispersibility of the agent in solution.

The stabilizing additives may be employed at a concentration ranging between about 0.1 and 5 % (W/V), preferably about 0.5 % (W/V). Suitable, but non-limiting, examples of stabilizing additives include gum acacia, gelatin, methyl cellulose, polyethylene glycol, and polylysine. The preferred stabilizing additives are gum acacia, gelatin and methyl cellulose.

The amount of active agent in the composition typically is a pharmacologically or biologically effective amount. However, the amount can be less than a pharmacologically or biologically effective amount when the composition is used in a dosage unit form, such as a capsule, a tablet or a liquid, because the dosage unit form may contain a multiplicity of carrier/biologically-active agent compositions or may contain a divided pharmacologically or biologically effective amount. The total effective amounts will be administered by cumulative units containing, in total, pharmacologically or biologically active amounts of biologically-active agent.

The total amount of biologically-active agent to be used can be determined by those skilled in the art. However, it has surprisingly been found that with certain biologically-active agents, such as calcitonin, the use of the presently disclosed carriers provides extremely efficient delivery. Therefore, lower amounts of biologically-active agent than those used in prior dosage unit forms or delivery systems can be administered to the subject, while still achieving the same blood levels and therapeutic effects.

The amount of carrier in the present composition is a delivery effective amount and can be determined for any particular carrier or biologically-active agent by methods known to those skilled in the art.

Dosage unit forms can also include any of excipients; diluents; disintegrants; lubricants; plasticizers; colorants; and dosing vehicles, including, but not limited to water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

Administration of the present compositions or dosage unit forms preferably is oral or by intraduodenal injection.

EXAMPLES

The invention will now be illustrated in the following non-limiting examples which are illustrative of the invention but are not intended to limit the scope of the invention.

EXAMPLE 1

GENERAL PROCEDURE FOR THE PREPARATION OF CARBOXYLIC ACID SODIUM SALTS

The carboxylic acid is stirred with a minimal volume of water at room temperature. The mixture is adjusted to pH 7-7.5 by the portionwise addition of 2N aqueous sodium hydroxide. The resulting clear solution is lypholyzed to give the desired carboxylic acid sodium salt as a white powder in quantitative yield.

EXAMPLE 2

PREPARATION OF CALCITONIN DOSING SOLUTION

Cyclohexanepropionic acid sodium salt (800 mg) was placed in a test tube. Distilled water (3 mL) was added. The mixture was stirred to effect solution and the pH was adjusted to between 7.0-7.6 with sodium hydroxide or hydrochloric acid. The volume of added acid or base was recorded. The total volume of the solution was brought to 4 mL by the addition of distilled water. Calcitonin (20 ug) was added to the solution. The final carrier concentration was 200 mg/mL and the final calcitonin concentration was 5 ug/mL.

A similar process was used to prepare all of the dosing solutions used in these carboxylic acid sodium salt experiments.

EXAMPLE 3

ORAL DELIVERY OF CALCITONIN TO RATS

For each sample, six fasted rats were anesthetized. The rats were administered, by oral gavage, one of the calcitonin/carrier dosages prepared as above. The calcitonin concentration in each sample was 1.5 ug/mL. Each rat was administered a dosage of two mL/kg. Blood samples were collected serially from the tail artery. Serum calcium was determined by testing with a Demand™ Calcium Kit (available from Sigma Chemical Company, St. Louis, Missouri, USA). The results of the test are illustrated in Figure 1.

EXAMPLE 4

PREPARATION OF HEPARIN DOSING SOLUTION

Cyclohexanepropionic acid sodium salt (900 mg) was added to 1,2-propanediol (4.5 mL) in a test tube and labelled Solution A. In another test tube, sodium heparin (300 mg) was added to a aqueous solution (4.5 mL) of 1.7N citric acid and 1.0% gum acacia and labelled Solution B. Both solutions were vortexed and heated in a water bath at about 37°C for 15 minutes. Solution A was then poured into Solution B giving a mixture having a pH of about 4-5. The final carrier concentration was 100 mg/mL and the heparin concentration was 33.3 mg/mL. The pH of this solution could be adjusted to neutral by the addition of 50 mTrizma® hydrochloride buffer.

Following a similar procedure, a sample having cyclohexane carboxylic acid (900 mg) and sodium heparin (300 mg) was prepared. The solution had a heparin concentration of 33.3 mg/ml.

ORAL DELIVERY OF HEPARIN TO RATS

EXAMPLE 5

For each sample, five fasted rats were anesthetized. The rats were administered, by oral gavage, one of the heparin/carrier dosages prepared in Example 4. The heparin activity in plasma was determined by use of the activated partial thromboplastin time (APTT; J.B. Henry, Clinical Diagnosis and Management by Laboratory Methods, Philadelphia: W.B. Saumders, 1979). The results of this test are illustrated in Figure 2.

EXAMPLE 6

Two samples having 300 mg/kg of cyclohexanepropanoic acid and 50/mg/kg of Heparin and 300 mg/kg of cyclohexanecarboxylic acid and 50 mg/kg of heparin, respectively, were prepared. These were administered by oral gavage to rats. The results are illustrated in Figure 3.

EXAMPLE 7

Three samples having 300 mg/kg of cycloheptanecarboxylic acid and 50 mg/kg of heparin and 300 mg/kg of cyclohexanecarboxylic acid and 50 mg/kg of heparin and 300 mg/kg of cyclopentanecarboxylic and 30 mg/kg of heparin, respectively, were prepared. These were administered by oral gavage to rats. The results are illustrated in Figure 4.

EXAMPLE 8

Three samples having 100 mg/kg, 300 mg/kg and 500 mg/kg of cyclohexanepropanoic acid and 25 mg/kg of heparin, respectively, were prepared. These were administered by oral gavage to rats. The results are illustrated in Figure 5.

EXAMPLE 9

Three samples having 300 mg/kg cyclohexanepropanoic acid and 25 mg/kg, 50 mg/kg and 100 mg/kg of heparin, respectively, were prepared. These were administered by oral gavage to rats. The results are illustrated in Figure 6.

EXAMPLE 10

Further compositions of carriers with heparin were prepared and tested. The results are in Table 1.

TABLE 1

HEPARIN CARRIERS	ACTIVITY (APTT X CONTROL) (mg/kg Carrier/mg/kg Hep) (300/100)	(300/50)	(300/25)
Cyclohexanecarboxylic acid	5.31	1.70	1.31
Cyclopentanecarboxylic acid	4.58	1.44	1.05
Cycloheptanecarboxylic acid	--	1.31	--
Hexanoic acid	4.77	1.38	--
3-Cyclohexanepropanoic acid	9.04	3.0	1.7
Methylcyclohexanecarboxylic acid	5.55	--	2.1
1,2-Cyclohexanedicarboxylic acid	1.8	--	--
1,3-Cyclohexanedicarboxylic acid	2.18	--	--
1,4-Cyclohexanedicarboxylic acid	1.68	--	--
1-Adamantanecarboxylic acid	--	2.43	1.00
Phenylpropanoic acid	--	2.48	1.2
Cyclohexanepentanoic acid	--	2.95	1.42
Cyclohexanebutanoic acid	--	4.2	1.3
Pentylcyclohexanoic acid	--	4.1	--

All patents, patent applications, literature publications and test methods cited herein are hereby incorporated by reference.

Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed disclosure. All such modifications are within the full intended scope of the appended claims.

WHAT IS CLAIMED IS:

1. A composition comprising;

(A) at least one biologically-active agent; and

(B) (a) a compound having the formula:

$$R—CO_2H$$

wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)-naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and naphthyl(C_2 to C_{10} alkenyl);

R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, $-CO_2R^1$, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1 to C_{10})alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl;

(b) a salt thereof; or

(c) a combination of (a) and (b).

2. The composition according to claim 1, wherein said biologically-active agent is selected from the group consisting of a peptide, a mucopolysaccharide, a carbohydrate, a lipid, a pesticide or any combination thereof.

3. The composition according to claim 1, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial naturetic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination thereof.

4. The composition according to claim 3, wherein said biologically-active agent comprises an interferon, interleukin-II, insulin, heparin, calcitonin, oxytocin, vasopressin, cromolyn sodium, vancomycin, DFO or any combination thereof.

5. The composition according to claim 4, wherein said biologically-active agent is calcitonin.

6. The composition according to claim 4, wherein said biologically-active agent is heparin.

7. The composition according to claim 6 for oral administration to an animal wherein component (A) comprises 25 mg of heparin per kg of animal and component (B) compries 300 mg of cyclohexanecarboxylic acid per kg of animal.

8. The composition according to claim 1, wherein R is C_3 to C_8 cycloalkyl.

9. The composition according to claim 8, wherein R is cyclohexyl, cyclopentyl and cycloheptyl.

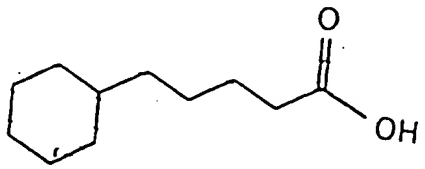
10. The composition according to claim 1, wherein R is C_6 to C_{12} alkyl.

11. The composition according to claim 8, wherein R is C_7 to C_{10} alkyl.

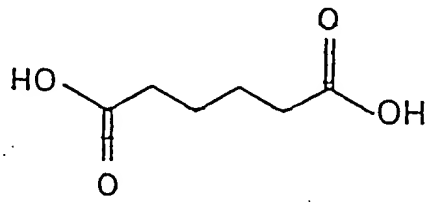
12. The composition according to claim 1, wherein R is substituted with alkoxy, -OH, or $-CO_2R^1$ wherein R^1 is hydrogen, C_1 to C_4 alkyl, or C_2 to C_4 alkenyl.

13. The composition according to claim 10, wherein R^1 is hydrogen.

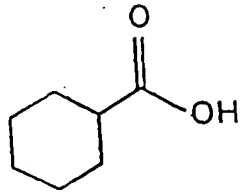
14. The composition according to claim 1, wherein (B) is a compound having the formula:



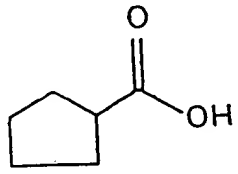
15. The composition according to claim 1, wherein (B) is a compound having the formula:



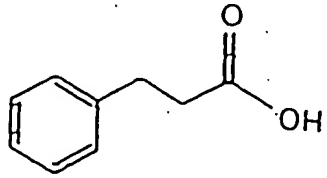
16. The composition according to claim 1, wherein (B) is a compound having the formula:



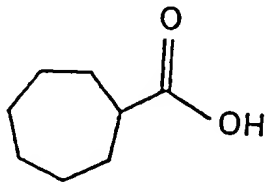
17. The composition according to claim 1, wherein (B) is a compound having the formula:



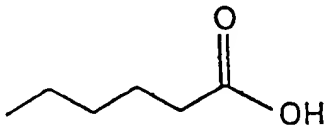
18. The composition according to claim 1, wherein (B) is a compound having the formula:



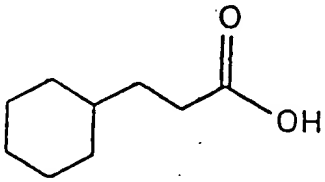
19. The composition according to claim 1, wherein (B) is a compound having the formula:



20. The composition according to claim 1, wherein (B) is a compound having the formula:



21. The composition according to claim 1, wherein (B) is a compound having the formula:



22. A dosage unit form comprising

(A) a composition according to claim 1; and

(B) (a) an excipient,

(b) a diluent,

(c) a disintegrant,

(d) a lubricant,

(e) a plasticizer,

(f) a colorant,

(g) a dosing vehicle, or

(h) any combination thereof.

23. A dosage unit form according to claim 20 comprising a tablet, a capsule, or a liquid.

24. A method for administering a biologically-active agent to an animal in need of said agent, said method comprising administering orally to said animal a composition as defined in claim 1.

25. A method for preparing a composition, said method comprising mixing:

(A) at least one biologically-active agent; and

(B) (a) a compound having the formula:

$$R—CO_2H$$

wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)-naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and naphthyl(C_2 to C_{10} alkenyl);

R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, $-CO_2R^1$, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1 to C_{10})alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl;

(b) a salt thereof; or

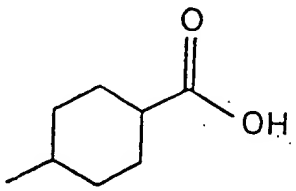
(c) a combination of (a) and (b).

(C) optionally a dosing vehicle.

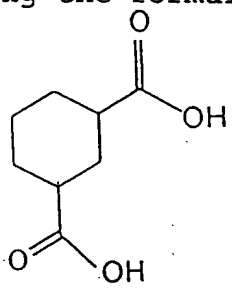
26. The method according to Claim 25, wherein a stabilizing additive is employed.

27. The method according to Claim 26, wherein the stabilizing additive is gum acacia, gelatin, polyethylene glycol or polylysine.

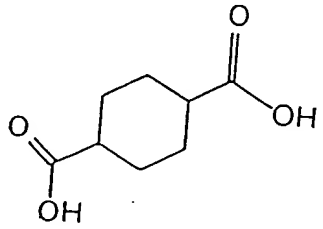
28. The composition according to claim 1, wherein (B) is a compound having the formula:



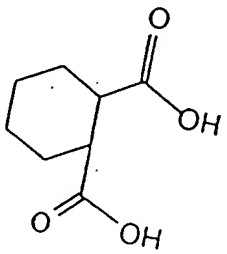
29. The composition according to claim 1, wherein (B) is a compound having the formula:



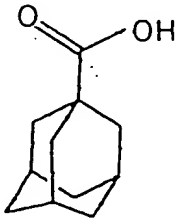
30. The composition according to claim 1, wherein (B) is a compound having the formula:



31. The composition according to claim 1, wherein (B) is a compound having the formula:



32. The composition according to claim 1, wherein (B) is a compound having the formula:



33. The composition according to claim 1, wherein (B) is a compound having the formula:

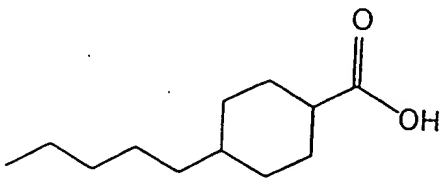


FIG. 1

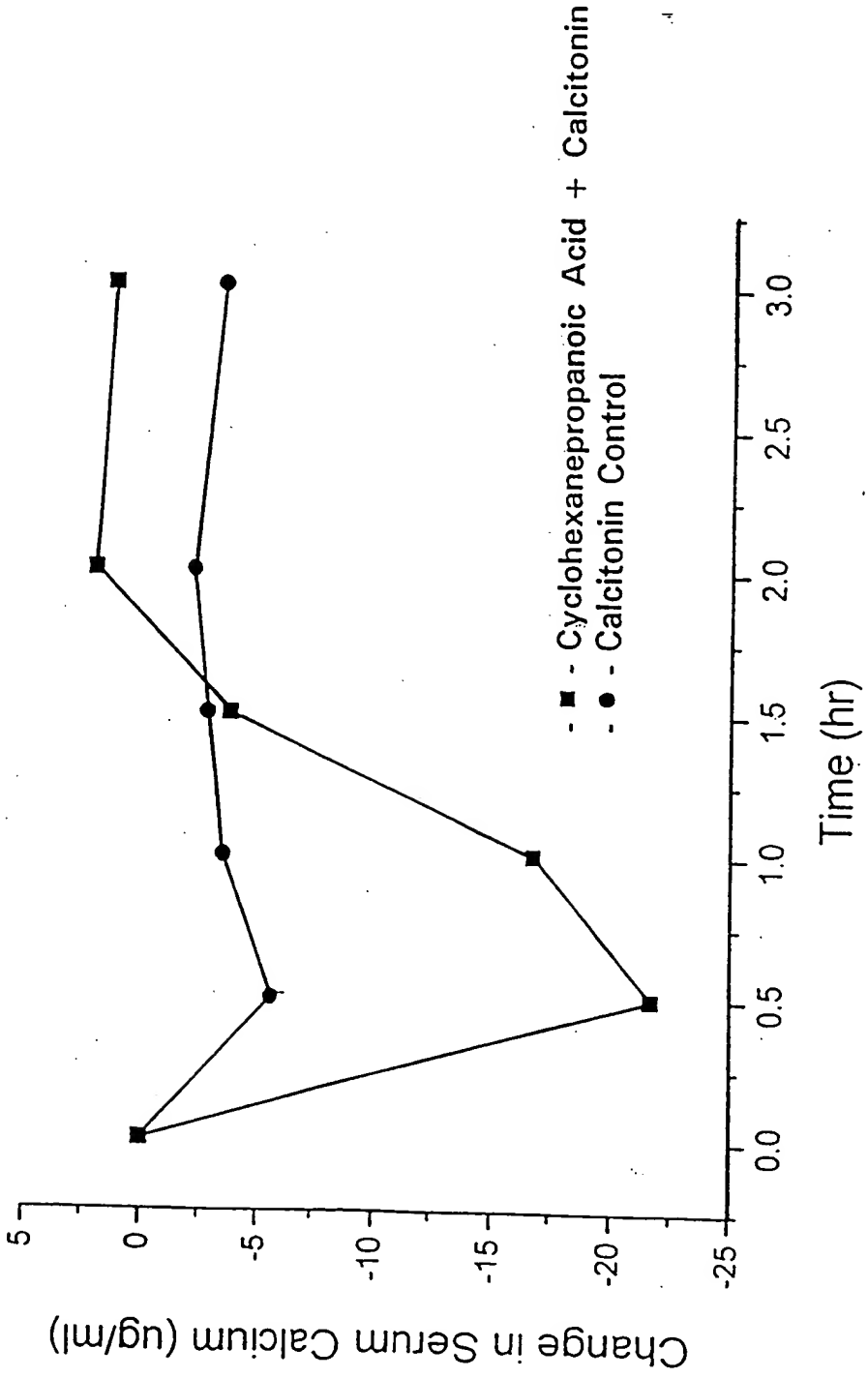

Change in Serum Calcium (ug/ml)
5
0
-5
-10
-15
-20
-25
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Time (hr)
- ■ - Cyclohexanepropanoic Acid + Calcitonin
- ● - Calcitonin Control

FIG. 2

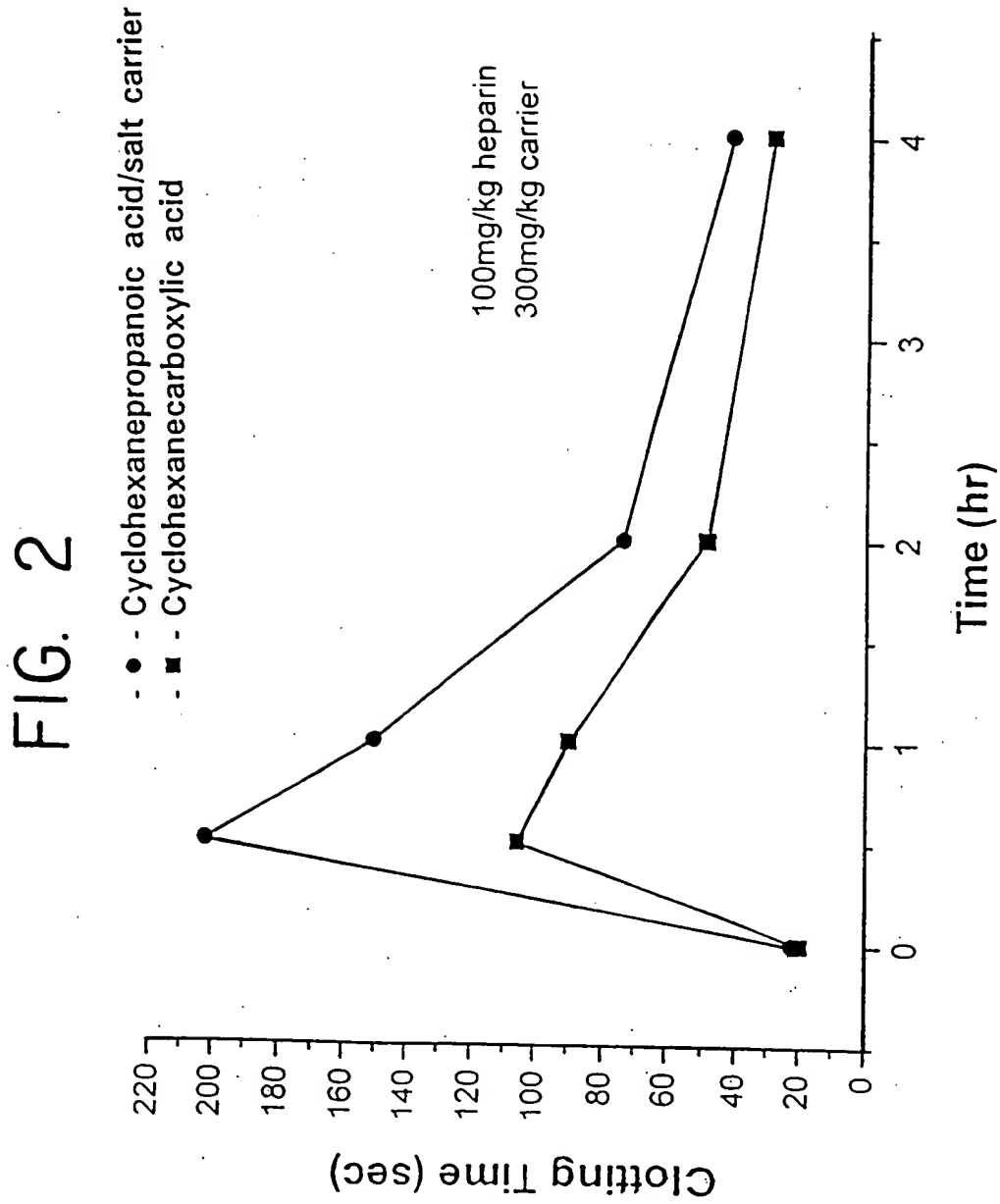

- ● - Cyclohexanepropanoic acid/salt carrier
- ■ - Cyclohexanecarboxylic acid
100mg/kg heparin
300mg/kg carrier
Clotting Time (sec)
Time (hr)
0
20
40
60
80
100
120
140
160
180
200
220
0
1
2
3
4

FIG. 3

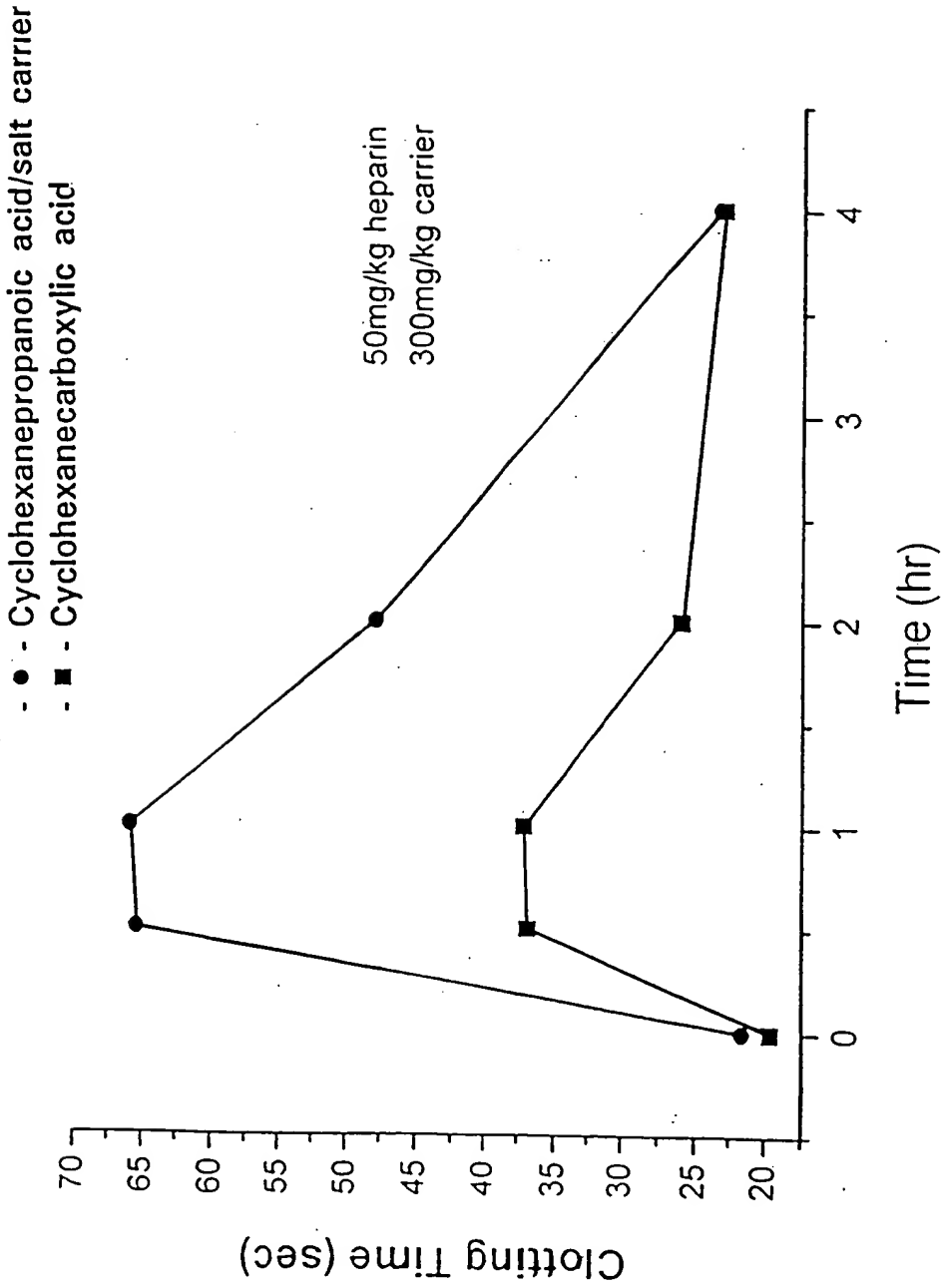

- ● - Cyclohexanepropanoic acid/salt carrier
- ■ - Cyclohexanecarboxylic acid
50mg/kg heparin
300mg/kg carrier
Clotting Time (sec)
70
65
60
55
50
45
40
35
30
25
20
0
1
2
3
4
Time (hr)

FIG. 4

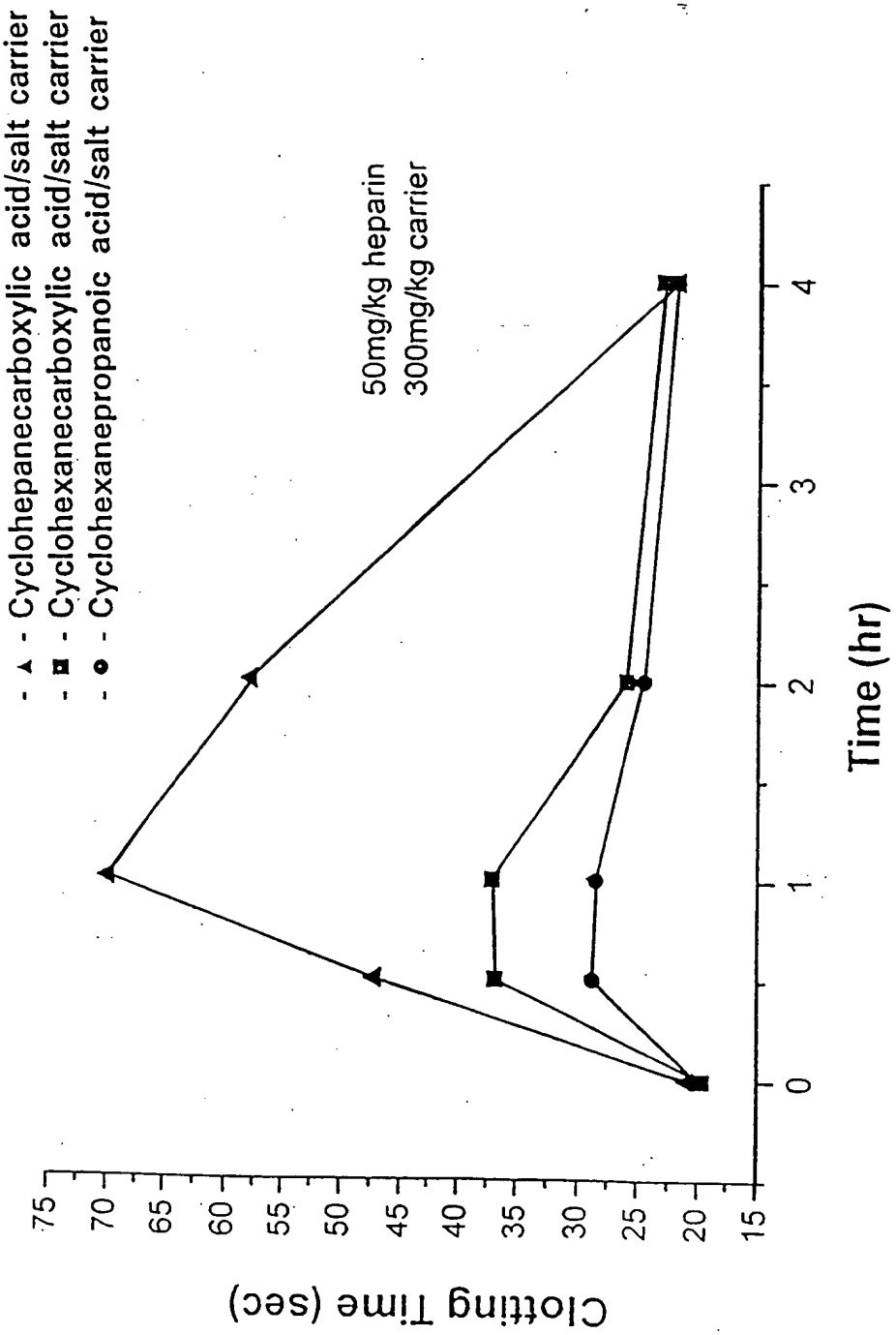

- ▲ - Cyclohepanecarboxylic acid/salt carrier
- ■ - Cyclohexanecarboxylic acid/salt carrier
- ● - Cyclohexanepropanoic acid/salt carrier
50mg/kg heparin
300mg/kg carrier
Clotting Time (sec)
75
70
65
60
55
50
45
40
35
30
25
20
15
0
1
2
3
4
Time (hr)

FIG. 5

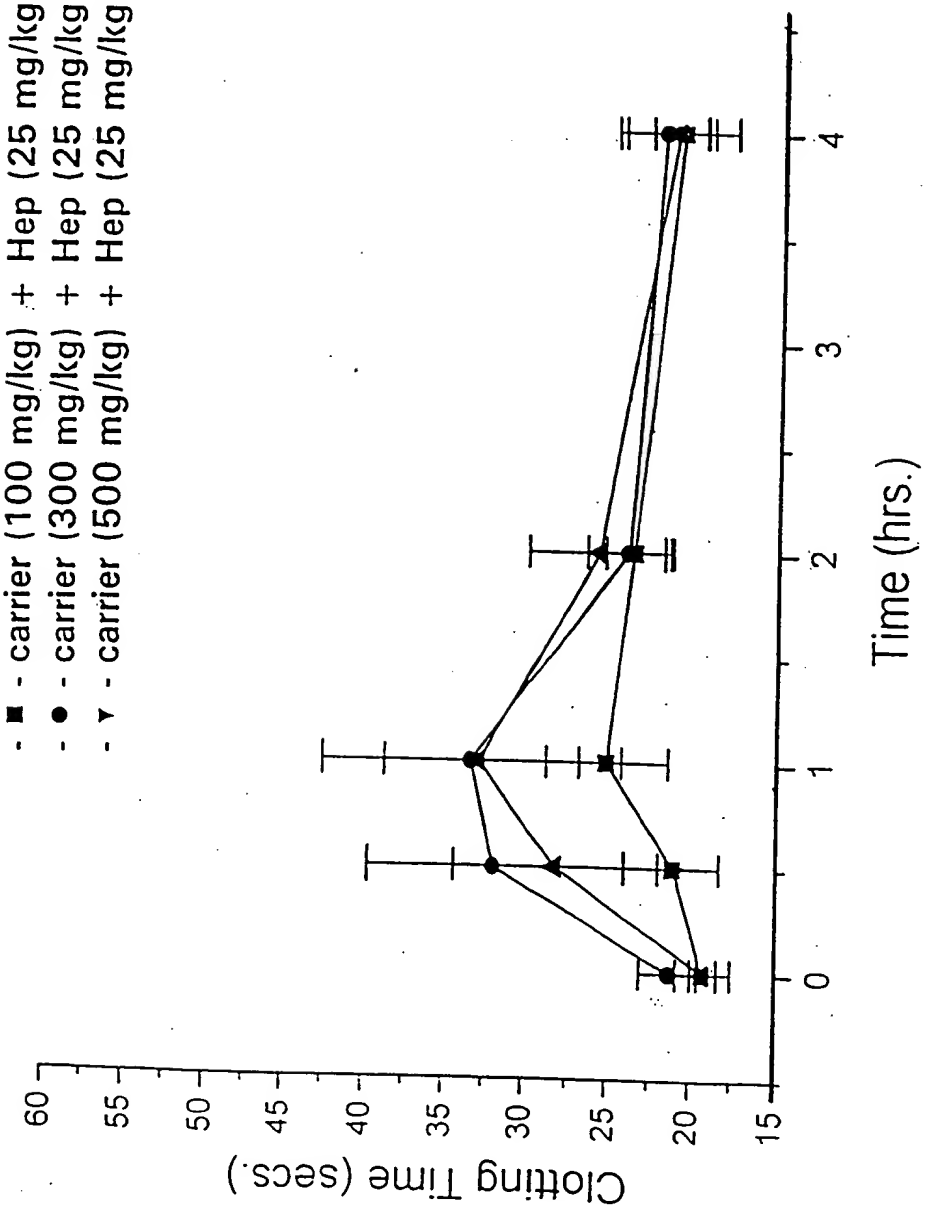
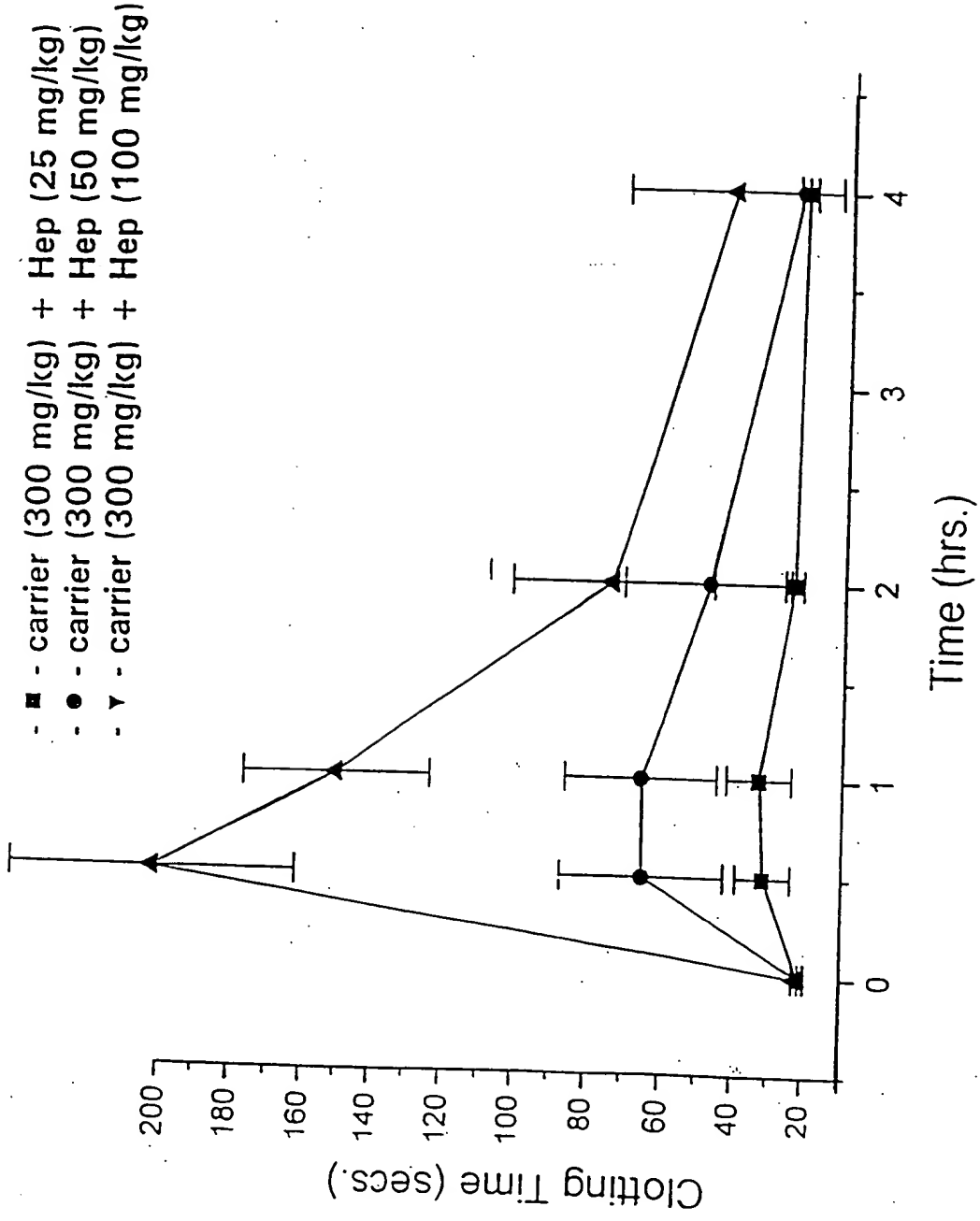

- ■ - carrier (100 mg/kg) + Hep (25 mg/kg)
- ● - carrier (300 mg/kg) + Hep (25 mg/kg)
- ▼ - carrier (500 mg/kg) + Hep (25 mg/kg)
Clotting Time (secs.)
60
55
50
45
40
35
30
25
20
15
0
1
2
3
4
Time (hrs.)

FIG. 6


- ■ - carrier (300 mg/kg) + Hep (25 mg/kg)
- ● - carrier (300 mg/kg) + Hep (50 mg/kg)
- ▼ - carrier (300 mg/kg) + Hep (100 mg/kg)
Clotting Time (secs.)
200
180
160
140
120
100
80
60
40
20
0
1
2
3
4
Time (hrs.)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/05110

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/19, 31/20, 31/70, 31/715, 38/16, 38/23, 47/12
US CL :514/2, 11, 12, 21, 56, 557, 570, 573, 574, 784
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 11, 12, 21, 56, 557, 570, 573, 574, 784

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

MERCK INDEX, 11TH ED.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS, MEDLINE, DIALOG
search terms: heparin, structures of claims 14, 16-19, 21, 28-33

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,462,991 (HIGUCHI ET AL) 31 July 1984, see the abstract, column 2, line 45 - column 3, line 4, column 3, line 62 - column 4, line 22, Example 1, claim 6.	1-5,12,13, 22-27
X	EP, A, 0,490,549 (ARVINTE ET AL) 17 June 1992, see the abstract, Example 4.	1-5,12,13 15,22-26
X	EP, A, 0,517,211 (TAKAMA ET AL) 09 December 1992, see page 3, lines 6-17, 29-41, and 57-58, and Experiment 1.	1-5,12,13, 15,20, 22-26
X	US, A, 4,708,952 (SALATINJANTS) 24 November 1987, see column 2, lines 41-48, column 3, lines 41-60.	1,20,22-26
X	US, A, 5,186,947 (GOETTSCHE ET AL) 16 February 1993, see Example 5.	1,2,8,9,16, 22,23,25

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
21 MAY 1995

Date of mailing of the international search report
14 JUL 1995

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIC `L SEARCH REPORT

`ternational application No.
PCT/US95/05110

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,442,090 (KAKEYA ET AL) 10 April 1984, see Table 6 and claim 1.	1-4,18,22, 23,25,28
X	US, A, 5,077,278 (HAFNER ET AL) 31 December 1991, see Example 10.	1,2,8,9,16, 17,19,21, 25
X	US, A, 5,039,481 (PACIFICI ET AL) 13 August 1991, see column 1, lines 18-21, and claim 1.	1,2,12,13, 29-31
X	JP, A, 56-68612 (HISAMITSU PHARM KK) 09 June 1981, see the abstract.	1,2,22-28, 33
X	US, A, 4,900,730 (MIYAUCHI) 13 February 1990, see the abstract, Example 10, claim 2.	1-5,12,13, 15,18,22, 23,25,31
X	Life Sciences, Volume 33, Number 1, issued 1983, Gelb et al, "Cycloamylose Complexation Of Adamantane Derivatives", pages 83-85, especially Table I.	1,2,25,32
X	Chemical Abstracts, Volume 83, issued 1975, Niyazov et al, "Solubility and dissociation constants of some alicyclic acids", page 342, column 1, abstract no. 184360k, Izv. Akad. Nauk Turkm. SSR, Ser. Fiz.-Tekh., Khim. Geol. Nauk, Number 4,issued 1975, pages 121-123, see entire abstract.	1,14,25
X	EP, A, 0,459,795 (NOMURA ET AL) 04 December 1991, see the abstract, page 4, lines 54-57, page 5, lines 5-17, Example 3, claims 4 and 5.	1-3, 12,13, 15,22-27
X	US, A, 5,250,236 (GASCO) 05 October 1993, see column 2, lines 21-68, and the examples.	1-5,10,11, 22,25,26
X	US, A, 4,895,725 (KANTOR ET AL) 23 January 1990, see examples 2 and 3.	1,2,22, 24-27
X	US, A, 3,795,739 (BIRKMAYER ET AL) 05 March 1974, see Examples 1-3.	1,2,12,13, 22-26
X	US, A, 3,794,561 (MATSUKAWA ET AL) 26 February 1974, see examples 8 and 10.	1,2,12,13, 22-26
X	WO, A, 93/18754 (FELDSTEIN ET AL) 30 September 1993, see Examples 2 and 3.	1-4,6,12, 13,22-26